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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/811,131 | 03/14/2001 | Christen M. Anderson | 660088.420D1 | 7827 |

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| EXAMINER | |
|---|---|
| SCHNIZER, HOLLY G | |
| ART UNIT | PAPER NUMBER |
| 1653 | |

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/811,131 | ANDERSON ET AL. | |
| | Examiner | Art Unit | |
| | Holly Schnizer | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *75-84 and 104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *75-84 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

### *Restriction/Election*

Applicant's election of Group X, claims 75-84 and 104 in the Response filed November 7, 2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Thus, the restriction requirement is FINAL.

### *Status of the Claims*

Claims 1-112 are pending. Claims 1-74, 85-103, and 105-112 have been cancelled. Claims 75-84 and 104 are pending and will be examined on the merits in this Office Action.

### *Rejections/Objections Withdrawn*

#### *Objection Withdrawn for Specification not in Sequence Compliance*

The objection to the Specification for lack of sequence identifiers for the sequences in Figures 1A, 1B, and 2 is withdrawn in light of the amendment to the Brief Description of the drawings.

#### *Claim Rejections - 35 USC § 112--Withdrawn*

The rejection of Claims 75-84, and 104 under 35 U.S.C. 112, second paragraph, for the acronym ANT is withdrawn in light of the amendment.

The rejection of Claim 84 under 35 U.S.C. 112, second paragraph for lacking an essential method step is withdrawn in light of the amendment.

***Claim Rejections - 35 USC § 103--Withdrawn***

The rejection of Claims 75, 78, 79, and 83 under 35 U.S.C. 103(a) as being unpatentable over Roux et al. (Anal. Biochem. (1996) 234: 31-37; ref. CM of IDS of Paper No. 6) in view of Adrian et al. (Mol. Cell. Biol. (1986) 6(2): 626-634; ref. AH of IDS of Paper No. 6) is withdrawn in light of Applicants arguments, the Declaration of Anderson under 37 C.F.R. 1.132, and two newly cited references; Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) and Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506). Hatanaka et al. disclose expression of human ANT1 in yeast. However, Hatanaka et al. teach that the N-terminal region of the human ANT polypeptide had to be replaced with the yeast sequence in order to achieve significant expression. Therefore, Hatanaka et al. provide evidence that recombinant expression of ANT was difficult and not routine. Heimpel et al. disclose the expression of an ANT from N. crassa in E. coli. Heimpel et al. state that yeast AAC2 and mammalian AAC (also referred to as ANT) are not expressed at significant levels in E. coli and that there is no evidence that the proteins are incorporated into E. coli membranes (p. 11504, Col. 1). Thus, Heimpel et al. provides additional evidence of failure to express mammalian ANT in E. coli. While both Hatanaka et al. and Heimpel et al. are post-filing references, they show that even after the filing date of the present invention, heterologous expression of ANT was not routine.

The rejection of Claims 75-79 and 83 under 35 U.S.C. 103(a) as being unpatentable over Roux et al. and Adrian et al. as applied to claims 75, 78, 79, and 83 above, and further in view of Tjaden et al. (J. Biol. Chem. (April 1998) 273(16): 9630-9636; ref. DL of Paper No. 6) is withdrawn in light of Applicants' arguments, the Anderson Declaration and Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) and Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506) for the same reasons as explained above.

## *Rejections Maintained*

### *Claim Rejections - 35 USC § 102--Maintained*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 104 is rejected under 35 U.S.C. 102(b) as being anticipated by Neumann et al. (J. Immunol. (1994) 152: 343-350).

A response to Applicants arguments follows the restatement of the rejection below:

Rejection:

Neumann et al. discloses 96-well ELISA plates comprising an immobilized ANT polypeptide for screening of candidate agents that bind to an ANT polypeptide

(antibodies). The immobilized ANT polypeptides of Neumann et al. are considered patentably indistinguishable from recombinant ANT polypeptides and also are considered variants of recombinant ANT polypeptides of other isoforms.

Response to Arguments:

Applicants argument that Neumann et al. does not teach each and every limitation of the claim has been considered but is not deemed persuasive for the following reasons:

*Absent evidence Non-recombinant proteins not distinguishable over recombinant*

Applicants argue that the ANT protein described in Neumann et al. is non-recombinant and therefore Neumann et al. does not teach the limitation that the ANT protein must be recombinant. Recombinant and non-recombinant refers to how the protein is made and therefore is considered a product by process (i.e. ANT made by recombinant expression). Product-by-process claims are not limited to the process of making that product, but only the structure implied by the steps (see MPEP 2113). In the present case, the non-recombinant ANT protein of Neumann et al. has the same structure and function as the recombinant ANT. Therefore, absent evidence to the contrary, it appears that the non-recombinant ANT is patentably indistinguishable from the recombinant ANT.

*Assay plate of Neumann et al. is indistinguishable from that of claim regardless of its intended use*

Applicants argue that Neumann et al. do not describe an assay plate for high throughput screening. This argument has been considered but is not persuasive

because the product claimed is not limited by its intended use unless the intended use changes the structure of the product. In the present case, the assay plate of Neumann et al. has all of the features of the assay plate claimed such as a plurality of wells wherein each well has an immobilized ANT that is at least 95% identical to SEQ ID NOs: 31, 32, or 33. Applicant argues that the assay plate of Neumann et al. does not contain sufficient ANT suitable for high throughput screening. This argument is not convincing because there is no evidence that the amount of ANT on the assay plates of Neumann et al. would be insufficient for high throughput screening.

*Bovine ANT is at least 95% identical to ANT2 and ANT3*

Bovine ANT is 98% identical to ANT2 and ANT3 (see sequence alignment attached). Furthermore, both ANT2 and ANT3 are expressed in the heart (the source of the Neumann et al. ANT protein). Therefore, absent evidence to the contrary, bovine ANT of Neumann et al. would be at least 95% identical to at least ANT 2 or ANT3.

Therefore, absent evidence of a distinguishable feature of the claimed assay plates, it appears that the assay plates of Neumann et al. meet the limitations of the present claim and the rejection is maintained.

## ***New Rejections***

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83 is rejected under 35 U.S.C. 102(b) as being anticipated by Roux et al. (Anal. Chem. (1996) 234: 31-37; ref. CM of IDS of Paper No. 6).

Roux et al. teaches a method for identifying an agent that binds to an adenine nucleotide translocator (ANT) polypeptide comprising contacting an agent (N-ATR or Mant-ATR) with beef heart mitochondria (a biological sample containing ANT) under conditions and sufficient time to permit binding and detecting binding by fluorescence (see p. 35-36). Bovine ANT is 98% identical to ANT2(SEQ ID NO: 32) and ANT3 (SEQ ID NO:33) (see sequence alignment attached). Both ANT2 and ANT3 are expressed in heart. Therefore, absent evidence to the contrary, the biological sample of Roux et al. contains an ANT that is at least 95% identical to at least ANT2 or ANT3 and the biological sample of Roux et al. is indistinguishable from recombinant ANT2 or ANT3. Therefore, Roux et al. is considered to disclose a method with identical methods steps (contacting an agent with a biological sample and detecting binding) as those of the claims using products that are indistinguishable from the claims (an ANT polypeptide that is at least 95% identical to SEQ ID NO:32 or 33).

This rejection could be overcome by adding the step of recombinant production of the ANT polypeptide to the claimed method.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent that binds to an adenine nucleotide translocator comprising contacting the candidate agent with a host cell expressing an adenine nucleotide translocator fusion protein comprising a polypeptide sequence fused to the N-terminus of an ANT polypeptide, wherein the ANT polypeptide comprises at least 95% identity to the amino acid sequences of the claims, does not reasonably provide enablement for methods wherein the host cell expresses a non-fusion ANT polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Undue experimentation would be required to develop recombinant expression of non-fusion ANT polypeptides having the claimed sequences that would be active (able to bind other proteins). Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

*Nature of the Invention and Breadth of the Claims includes recombinant expression of unmodified ANT polypeptides:*

The invention involves a method for screening for agents that bind ANT polypeptides. The method involves contacting the agent with a host cell that expresses or a biological sample containing a recombinant polypeptide having at least 95% identity to the sequences of ANT1 (SEQ ID NO:31, ANT2 (SEQ ID NO:32), or ANT3 (SEQ ID NO:33). Thus, the claim encompasses methods requiring a host cell that expresses or a biological sample that contains a recombinant non-fusion ANT polypeptide.

*State of the prior art and relative skill of those in the art-- expression of active ANT unsuccessful without modification of ANT sequence:*

The Anderson Declaration filed November 7, 2003 provides evidence of the relative skill and state of the prior art. Fiermonte et al. (Biochem. J. (1993) 294: 293-299) (discussed in the Anderson Declaration) teach that attempts to recombinantly express ANT in E. coli did not result in detectable levels of mammalian ANT polypeptides. The post-filing reference of Heimpel et al. (J. Biol. Chem. (2001) 276(15): 11499-11506) provides evidence that that those of skill in the art even at the time and after the filing date of the present invention did not know how to express a functional ANT in E. coli. Heimpel et al. state that attempts to express human ANT1 in E. coli were unsuccessful and evidence of ANT membrane expression in the E. coli was not found (p. 11504, Col. 1, 2nd paragraph). Miroux et al. (J. Mol. Biol. (1996) 260(3): 289-298)(discussed in the Anderson Declaration) successfully expresses recombinant ANT in E. coli, however, it appears that the expressed ANT accumulates in inclusion bodies

where it is unfolded and inactive. Hatanaka et al. (Biol. Pharm. Bull. (2001) 24(6): 595-599) discloses that in order to get successful expression of human ANT1 in yeast, the first 11 residues of the human N-terminal sequence had to be replaced with the corresponding 26 residues of the yeast AAC2 (see p. 597, Col. 1). Such a modification would make the human ANT1 less than 95% identical to ANT1 of SEQ ID NO: 31. Therefore, as a whole it appears that the state of the art and those of skill in the art did not know of a method to express an active ANT (one that would be able to bind) in E. coli and did not know of a method to express an active ANT in yeast without some type of modification of the N-terminal sequence.

*Direction/Guidance and working examples only describe expression of ANT fusion proteins:*

The present Specification only describes and provides examples for successful expression of ANT polypeptides fused at the N-terminus to a his-tag sequence (containing 6 histidines at the N-terminus of ANT sequence) or GST (Glutathione-S-transferase) in various cell types. The Specification does not provide any examples or guidance of expressing ANT polypeptides without fusion of an additional sequence to the N-terminus.

*Expression of non-fusion ANT polypeptides highly Unpredictable:*

Given the difficulties and lack of success in the prior art and the lack of guidance or examples in the present Specification discussed above and the lack of knowledge of the source of the problem in ANT expression, determination of what method steps

would be required to successfully express the claimed ANT polypeptides without an N-terminal fusion is highly unpredictable.

*Undue Experimentation would be required:*

To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the discovery of a method that would allow successful recombinant expression of an unmodified and active ANT. Such a discovery would constitute undue experimentation. Thus, for the reasons described above, the full scope of the claims is not considered enabled.

## ***Conclusions***

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Tuesday, Thursday, and Friday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
February 7, 2004

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